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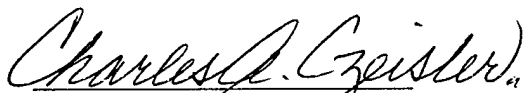
PROGRESS REPORT

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CLINICAL TRIAL OF THE EFFECT OF EXERCISE ON ENDOGENOUS CIRCADIAN PERIOD, SLEEP AND PERFORMANCE

Grant Number: F49620-94-1-0398

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1. Cover Page:

2. Objectives:

The objectives of the research effort *have not changed*; they remain as follows:

Specific Aim 1: Test the hypothesis that exercise alters the intrinsic period of the endogenous circadian pacemaker that drives circadian rhythms in alertness, cognitive performance and sleep tendency.

Specific Aim 2: Test the hypothesis that sleep latency and efficiency as well as waking alertness and cognitive performance deteriorate at adverse circadian phases when the sleep-wake cycle is scheduled to a 20-hour day on a forced desynchrony protocol. This is equivalent to traveling in an eastward direction across four time zones each day, thus providing an experimental model for the dyssomnia of chronic transmeridian travel.

Specific Aim 3: Test the hypothesis that exercise during the forced desynchrony protocol results in decreased sleep latency, reduced nocturnal sleep disruption, improved sleep efficiency, and increased sleep intensity as measured by the delta power density of the sleep EEG, as compared to sleep following sedentary activity.

Specific Aim 4: Test the hypothesis that exercise during scheduled waketimes will also enhance daytime alertness, performance and short term memory, particularly following sleep episodes scheduled at adverse circadian phases.

3. Status of Effort:

We proposed to study three subjects per year over three years for a total of nine research subjects. In the period covering 9/94 -8/97, we have empaneled ten research subjects for a total of 373 subject days. Of the ten subjects, eight have completed the entire 44-day research protocol. As described below, we have added the new data derived from the studies completed in the third year of the research project to the data obtained from the studies completed in years one and two of the research project. These data include: minute-by-minute samples of core-body temperature; hourly blood plasma samples; neurobehavioral testing including the reaction time task (psychomotor vigilance test); nightly polysomnographic recordings; subjective assessment of sleep quality questionnaires; and multiple daily exercise sessions (monitoring average power, RPM, distance cycled, calories burned, heart rate); and urine samples every three hours.

4. Accomplishments/New Findings:

Data derived from the studies were separated by condition (exercise or control) and folded at either the period of the sleep-wake cycle (20 hours) or at the intrinsic circadian period of the endogenous circadian temperature cycle in order to assess the effect of exercise on the homeostatic and circadian components of these rhythms.

As described above, core body temperature data from the two subjects studied in the third year of the project have been added to the cohort. Examination of the data derived from all eight subjects indicates that there is not a significant difference in the period of the endogenous circadian pacemaker between the exercise and control conditions which is consistent with our preliminary findings during the first two years. This exciting result indicates that under forced desynchrony conditions, the human circadian pacemaker oscillates with a remarkably stable period, such that the observed intrinsic period of the endogenous core body temperature rhythm does not change despite the physiologic concomitants of aerobic exercise. Because exercise was scheduled to occur at nearly all circadian phases, these results suggests exercise does not exert a parametric effect on the endogenous circadian pacemaker. This would imply that reports of exercise-induced phase delay shifts of the human circadian pacemaker could not have been attributed to an exercised-induced lengthening of circadian period.

Analysis of the effects of the 45-minute exercise bouts on core body temperature during waking episodes revealed that the average temperature during the exercise condition was significantly higher than that which occurred during the control condition. Analysis of the core body temperature data during sleep episodes revealed that the average temperature curve for the exercise condition was significantly different than that observed during the control condition. The average temperature was lower in the exercise condition when sleep occurred on the descending limb and particularly at the nadir of the circadian cycle. The average temperatures during sleep were approximately the same when sleep occurred on the ascending limb and the crest of the circadian cycle. These results are consistent with those obtained during years one and two of the project and suggest that there is a circadian variation in the thermoregulatory response to exercise during the subsequent sleep episode.

Analysis of the reaction time data in four of the eight subjects continues to be promising. These data revealed significant differences between the exercise and control conditions. Average data folded at the observed endogenous circadian period revealed that the median and optimal reaction time (fastest 10% of responses) were significantly improved in the exercise as compared to the control condition across all phases of the circadian cycle. Comparison of the average difference between conditions revealed that the greatest exercise-associated improvement in median reaction time occurred around the nadir of the core body temperature cycle where neurobehavioral

deficits are known to be the greatest. Interestingly, closer examination of the data reveals that even at adverse phases of the core body temperature cycle (around the nadir), median reaction time is just as rapid in the exercise condition as it is at the most favorable circadian phases of the core body temperature cycle (around the crest) in the control condition. These preliminary results suggest that there may be an "exercise-induced activation" of neurobehavioral functioning as reflected by visual reaction time. However, final confirmation of this result will await completion of the cohort. This result is particularly interesting given the fact that we have not found a difference in the subjective mood scale and performance data between conditions thus far. Subjective mood and cognitive performance data were folded at the observed period of the core body temperature rhythm, which as expected, revealed a significant circadian variation in alertness and cognitive performance (number of calculations attempted on an addition test). These rhythms paralleled core body temperature, and reached their minimum just after the nadir of the cycle. Similarly, folding the data at the period of the subject's sleep/wake cycle indicated a homeostatic decline in alertness and performance as length of prior wakefulness increased. However, as stated above, there were no significant differences when the data were separated by condition. Thus, the effects of exercise may be specific to pathways mediating visual reaction time tasks.

In summary, the addition of the research studies conducted in year three of the project solidifies the notion that regular bouts of aerobic exercise affect the physiology of the thermoregulatory system in a phase-dependent manner. Preliminary results from the reaction time data continue to be extremely promising. These data suggest that aerobic exercise may have the potential to enhance neurobehavioral performance, as reflected by simple visual reaction time, particularly at the nadir of the temperature cycle where neurobehavioral deficits are known to be the greatest.

5. Personnel Report:

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|-------------------------------------|---------------------------------|
| 1. Charles A. Czeisler, Ph.D., M.D. | Associate Professor of Medicine |
| 2. David W. Rimmer, M.S. | Senior Research Assistant |
| 3. Gerald A. Jayne | Senior Research Technician |
| 4. Elizabeth Higgins | Research Assistant |

6. Publications:

Rimmer DW, Dijk DJ, Wyatt JK, Dinges DF, Czeisler CA. Exercise of moderate intensity can improve visual reaction time. New England Chapter of the American College of Sports Medicine Annual Meeting, 1997.

Rimmer DW, Czeisler CA. Exercise of moderate intensity does not affect the period of the endogenous circadian pacemaker. *Sleep Research*, 26:749, 1997.

7. Interactions/Transitions:

A. Participation/presentations:

CA Czeisler:

1. February 2-4, 1997:
National Institute of Aging/NASA Workshop on Aging and Spaceflight.
2. June 12-15, 1997:
Scientific Keynote Address, 11th Annual Meeting, Association of Professional Sleep Societies. San Francisco, CA.

DW Rimmer:

1. June 1997:
Eleventh Meeting of the Association of Professional Sleep Societies (APSS).
San Francisco, CA.
2. September 1997:
Annual Meeting of the American College of Sports Medicine (New England Chapter). Providence RI.

B. Consultative and advisory functions:

CA Czeisler:

1. January 1994:
AFOSR/NL Night Operations/Human Chronobiology Workshop, Brooks Air Force Base, TX. Dr. Genevieve Haddad, Organizer.
2. May 7-9, 1995
AFOSR, Aerospace Medical Association Meeting, Anaheim, CA. Dr. Levy, Organizer.
3. June 6-7, 1995:
AFOSR, Night Operations/Human Chronobiology Workshop #3, Bolling Air Force Base, VA. Dr. Genevieve Haddad, Organizer.
4. July 31, 1995
AFOSR/PRET Conference, University of Pennsylvania.
Dr. David Dinges, P.I.
5. November 2-3, 1995:
National Transportation Safety Board/NASA Conference on Fatigue in Transportation. Honorable James Hall, NTSB Chairman, and Dr. Mark Rosekind, NASA, Co-Organizers.

6. August 1, 1996:

AFOSR/PRET Consultation, Boeing Commercial Aviation, Seattle, WA.
Dr. Genevieve Haddad, Dr. Curtis Graeber, Organizers.

7. June 1997:

AFOSR/PRET Conference, San Francisco, CA.
Dr. David Dinges, P.I.

C. Transitions:

Data from these experiments will be incorporated into a model of alertness and performance currently being developed to counteract fatigue associated with Air Force missions. The model is being developed through the support of the AFOSR Partnership for Research Excellence and Transition Program (PRET), Center on Countermeasures for Jet Lag and Sleep Deprivation organized at the University of Pennsylvania.

8. New discoveries, inventions, or patent disclosures:

None

9. Honors/Awards:

CA Czeisler:

-Plenary Address, Japanese Sleep Research Society, Sapporo, Japan (1996).

-Elected to the Association of American Physicians (1997).

-Keynote Speaker, Associated Professional Sleep Societies Annual Meeting, San Francisco, CA (June 1997).

DW Rimmer:

-SRS Trainee Travel Award to the Eleventh Meeting of the Association of Professional Sleep Societies (APSS) in San Francisco, CA. (1997).